E1 1. **(Amended)** A method for identifying a substance which inhibits an infection or the result of an infection of an animal or human cell targeted by hepatitis C virus or any other virus which uses lipid globules, said method comprising:

a) providing a lipid globule targeting sequence, as a first component;

b) providing a lipid globule, as a second component;

c) contacting the two components with a substance to be tested under conditions that would permit the two components to interact in the absence of the substance; and

d) determining whether the substance disrupts the interaction between the first and second components;

wherein the targeting sequence comprises a hepatitis C virus (HCV) core protein or a fragment, variant or homologue thereof wherein said fragment, variant or homologue binds to the lipid globule.

2. **(Amended)** A method according to claim 1 wherein the substance to be tested is administered as a peptide to a cell, the lipid globule targeting sequence is recombinantly or naturally expressed in said cell and the lipid globule is a natural constituent of said cell.

E2 3. **(Amended)** A method according to claim 2 further comprising:

e) contacting a virus or infective viral polynucleotide with a cell, wherein viral polynucleotide enters the cell in the absence of said substance which has been determined to disrupt the interaction between the first and second components;

f) contacting a virus or infective viral polynucleotide with a cell, wherein viral polynucleotide enters the cell in the presence of said substance and

g) determining if said substance reduces or abolishes the susceptibility of the cell to the effects of viral infection.

4. **(Amended)** A method according to claim 1 wherein the lipid globule targeting sequence comprises amino acids of the HCV core protein selected from the group consisting of 125 to 144, 161 to 166, and the combination thereof.

E3

5. **(Amended)** A method for identifying a substance for treating or preventing the effects of an infection of an animal or human cell targeted by hepatitis C virus or any other virus which uses lipid globules, which method comprises:

determining whether said substance can upregulate expression of adipocyte-specific differentiation related protein (ADRP) in a mammalian cell, by the following:

administering said substance to said mammalian cell; and

identifying whether the administration of said substance upregulates expression of adipocyte-specific differentiation related protein (ADRP).

E4

6. **(Amended)** The method according to claim 1 wherein the infection is a hepatitis infection.

E5

17. **(Amended)** The method according to claim 5 wherein the infection is a hepatitis infection.

Please add new Claims 22-25.

E6

22. The method according to claim 1 wherein the substance to be tested is administered to a cell, the lipid globule targeting peptide is recombinantly expressed in said cell and the lipid globule is a natural constituent of said cell.

23. The method according to claim 2 wherein the said recombinant means comprises transfection or transformation.

24. The method of claim 5 wherein said administering is by expressing the substance in the cell.

25. The method of claim 5 wherein said administering is by adding the substance to the cell in the media.

REMARKS

Claims 7 and 18 have been canceled without prejudice. Claims 1-6 and 17 have been amended to clearly define the present invention. Support for amended Claim 1 can be found in the specification on page 5, lines 3-4, page 7, lines 17-26, page 22, lines 23-26 and page 49, lines

10-13. Support for amended Claim 2 can be found in the specification on page 14, line 5 and on page 15, lines 2-4. Support for amended Claim 3 can be found in the specification on page 33, lines 20-28. Support for amended Claim 4 can be found in the specification on page 8, lines 7-13. Support for amended Claim 5 can be found in the specification on page 3, line 28 to page 4, line 2 and page 53, lines 4-5. Claims 6 and 17 have been amended to recite the type of infection as a hepatitis infection. Support for new Claim 22 can be found in the specification on page 14, lines 4-5. And support for new Claim 23 can be found in the specification on page 20, line 1 through page 21, line 4. No new matter has been added herewith.

The changes made to the claims by the current amendment, including **[deletions]** and additions, are shown on an attached sheet entitled **VERSION WITH MARKINGS TO SHOW CHANGES MADE**, which follows the signature page of this amendment.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected Claims 1-3, 6 and 7 under 35 U.S.C. § 112, first paragraph, because the Examiner believes that the specification does not reasonably provide enablement for "all fragments, derivatives, variants or homologues thereof" for the targeting sequence of the hepatitis C virus (HCV) core protein.

However, Claim 1 has been amended to read "a hepatitis C virus (HCV) core protein or a fragment, variant or homologue thereof wherein said fragment, variant or homologue binds to the lipid globule". Applicants respectfully submit that one of skill in the art would know how to produce a targeting sequence of the HCV core protein or a fragment, variant or homologue thereof, wherein said fragment, variant or homologue binds to the lipid globule based on the extensive teaching in the specification as well as knowledge of one of skill in the art. The specification makes clear which two regions are necessary for activity. Specifically on page 8, lines 7-13 of the specification recites that: "HCV core protein fragments of the invention contain both amino acids 125 to 144 and 161 to 166" (this is recited again in Example 3 on page 47, lines 15-27). The specification clearly identifies these as the lipid binding regions of the HCV core protein. In addition, the specification on page 18, line 6 through page 19, line 4 contains different methods of obtaining variants and homologues of the HCV core protein sequence. Therefore, one of skill in the art would know that a variant or homologue would need to posses both of these identified fragments to be "capable of binding to a lipid globule".

In addition, the specification provides one of skill in the art with the teaching to identify or produce a variant which is "capable of binding to a lipid globule". For example, a variant of the HCV core protein could be produced or identified based on the knowledge that certain allowable conservative amino acid changes could be made within the identified lipid globule association regions and more radical changes could be made in other regions to produce an active variant. On page 13, lines 7-16 and the corresponding table in the specification, examples of conservative amino acid changes are provided.

A homologue could be identified by one of skill in the art, based upon the nucleotide guidelines provided in the specification and computer programs to assess % homology within the identified regions in order to identify a homologue of the HCV core protein. One of skill in the art would realize that such a homologue would necessarily possess a higher homology within the lipid globule association regions than outside of the regions as noted on page 9, lines 8-12 of the specification. Additional guidance as to acceptable homology can be found in the specification on page 16, line 27 to page 17, line 4 where it states acceptable homology values for a homologue of the HCV core protein and page 17, lines 1-4 is very specific as to how much homology is preferred. In addition, on page 16, lines 1-6 of the specification it is stated that the nucleotide changes of the target sequence need to result in an active lipid targeting protein. Therefore, the specification provides ample guidance to one of skill in the art to produce and identify a homologue of the HCV core protein.

In view of the above arguments, Applicants respectfully request withdrawal of the rejection of Claims 1-3, 6 and 7 under 35 U.S.C. § 112, first paragraph.

The Examiner has rejected Claims 1-7, 17 and 18 under 35 U.S.C. § 112, first paragraph, because the Examiner believes that although the specification is enabling for the effect of a substance to reduce or abolish susceptibility of liver cells to HCV, it does not cover other viral infections in other cell types.

However, Applicants have amended Claim 1 to specify an animal or human cell targeted by hepatitis C virus or any other virus which uses lipid globules. Therefore, amended Claim 1 now indicates that the susceptibility is to HCV or any virus which uses lipid globules and that the target cells are any cells infected by these viruses. It is clear that HCV does not just target liver cells (Barba et al. 1997. Proc. Natl. Acad. Sci. 94:1200-1205, Abstract), therefore, the method

of the present invention could be used to identify a substance which inhibits infection of any cell which the virus might infect.

In light of the above argument, Applicants respectfully request withdrawal of the rejection of Claims 1-7, 17 and 18 under 35 U.S.C. § 112, first paragraph.

The Examiner has rejected Claims 5, 17, and 18 under 35 U.S.C. § 112, first paragraph because the Examiner believes that the specification fails to provide any evidence that any substance identified by the methods disclosed would prevent or elicit a therapeutic response in a viral infection.

Applicants respectfully submit that the specification provides evidence that the association of the HCV core protein with lipid globules leads to a decrease in the protein, ADRP. In addition, the specification provides extensive proof that ADRP is involved in prevention or reducing the symptoms of an infection (See Examples 4 and 5, on page 48, lines 31 through page 49, line 1, page 49, lines 7 - 14, from page 40, line 30 to page 50, line 3 and page 50 lines 10-12). In those examples, it is shown that ADRP levels correlate with the presence of an HCV infection and that the levels of ADRP consistently decreased when HCV was present in the cell. In addition, it is known that HCV associates with lipid globules within cells and that this process is associated with the infection and symptoms of the disease. ADRP is also shown to be associated with lipid globules (see page 2 lines 1-2 and 17-18). This then provides a basis for the experimental association and suggests that by increasing the amount of ADRP, the amount of HCV which may necessarily associate with the lipid particles decreases and the infection and/or symptoms of the infection decrease. Therefore one of skill in the art would understand that a substance which causes an increase in ADRP levels would correlate with a decrease or inability to detect HCV, eliciting a therapeutic response. The specification is enabling for such a method and substance.

Therefore, the Applicants respectfully request withdrawal of the rejection to Claims 5, 17, and 18 under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected Claims 1-7, 17 and 18 under 35 U.S.C. § 112, second paragraph because the Examiner asserts that the Applicants failed to point out and distinctly claim the subject matter which is regarded as the invention.

The Examiner has rejected Claims 1-3 and 6-7 for being vague and indefinite in the use of the terms "derivatives", "homologues" and "variants". However, Claim 1 has been amended to eliminate the term "derivatives". In addition, Claim 1 has been amended to state wherein said fragment, variant or homologue binds to a lipid globule. In addition, the terms variant, homologue and fragment have been defined in the specification specifically in terms of "binding to a lipid globule". Therefore, the definition of the terms are clear.

The Examiner further rejected the use of the terms "capable of" and "affecting" in Claim 1. However, claim 1 has been amended to state that the function of the substance is to inhibit an infection or result of an infection. Support for this amendment to Claim 1 is found on page 33, lines 20-28 which refers to examples of assaying levels of viral infection and page 53, lines 19-20 which further clarifies that the result is a reduction in viral titer. Therefore, amended Claim 1 states what the metes and bounds of the claimed invention is.

The Examiner believes that the terms "expressed" and "administered" in Claim 2 are indefinite. However, Claim 2 has been amended to read "administered as a peptide" and "recombinantly or naturally expressed". Support for the amendments can be found on page 14, line 5, where specification refers to the lipid globule targeting sequenced being expressed recombinantly in the cell and page 15, lines 2-4 which indicates that a naturally occurring peptide (ADRP) can also act as a lipid globule targeting sequence. In addition, page 29, line 28 through page 30, line 6 of the specification reveals that the candidate substance is a peptide, and one of skill in the art would know which methods are available to introduce a peptide into a cell. The specification gives examples for "administering" on page 28, line 28 through page 29 line 3.

The Examiner also objected to the term "administered" in Claim 3. In addition, the Examiner believes that the phrase "the susceptibility of the cell to viral infection or the effects of viral infection" is unclear. However, Claim 3 has been amended to clarify the methodologies employed in administering a virus to a cell. On page 42, lines 11-23 and page 45, lines 7-14 of the specification method for introducing viral polynucleotides to cells are detailed, and one with skill in the art would know which methods to utilize in order to introduce the viral

polynucleotides into the desired cell. Claim 3 has been amended to recite "determining if said substance reduces or abolishes the susceptibility of the cell to the effects of viral infection". There is clear support for this language in the specification. On page 33, line 20-28 the criteria for determining when a cell is "infected", both *in vitro* and *in vivo*, is stated. Specifically, on page 49, line 25-28 it is revealed in Example 5 how the infection of the cell can be determined using detection of the core protein. Page 54, line 14-20 gives an example of a method of determining HCV replication in infected chimpanzees. These methods reveal the "effects of viral replication" of the cell which can be determined *in vivo* or *in vitro*.

The Examiner believes the term "and/or" is indefinite in Claim 4. However, Claim 4 has been amended to state that the lipid globule targeting sequence comprises amino acids of the HCV core protein selected from the group consisting of 125 to 144 ,161 to 166, and the combination thereof. Support for this amendment has been noted in the above 35 U.S.C. § 112, first paragraph argument.

The Examiner has objected to Claims 5, 17 and 18 because the active method steps required to perform the claimed invention are not clearly set out. However, Claim 5 has been amended to further elucidate the method involved for treating or preventing the effects of a viral infection by stating: "determining whether said substance can upregulate expression of adipocyte-specific differentiation related protein (ADRP) in a mammalian cell, by the following: administering said substance to said mammalian cell; and identifying whether the administration of said substance upregulates expression of adipocyte-specific differentiation related protein (ADRP)". Therefore, the active steps have been clearly set out. Support for the amendment as well as new claims 24 and 25 can be found in the specification as follows: The assay methods for identifying a substance according the invention are disclosed in the specification beginning on page 24, line 11 through page 34, line 24. Specifically, page 32, line 21 to page 34, line 18 detail how to use the identified substances for their anti-viral activity. Examples of substances capable of upregulating expression of ADRP are found on page 34, line 30 to page 35, line 5. The specification also contains assaying methods on page 51, line 18 to page 54, line 20. These methods include both *in vitro* and *in vivo* methods, including methods to assess the effect of the candidate substances in transgenic animals and HCV-infected chimpanzees.

In view of the above arguments, Applicants respectfully request withdrawal of the rejection to Claims 1-7, 17 and 18 under 35 U.S.C. § 112, second paragraph.